American Chemistry Council
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October 14, 2005 CONTAIN NO CBI

8EHQ-1005-16261

TSCA Document Control Office (7407)
EPA East Building, Room 6428
1201 Constitution Avenue NW
Washington DC 20460
Attn: TSCA Section 8(e) Coordinator

Re: Draft Benzene Tier 1 VCCEP Risk Assessment (CASRN 71-43-2)

Dear Sir or Madam:

The American Chemistry Council's Benzene, Toluene & Xylenes (BTX) Voluntary Children's Chemical Evaluation Program (VCCEP) Consortium (the "Consortium"), on behalf of its members,[1] is submitting the enclosed contractor-prepared draft benzene Tier 1 VCCEP children's risk assessment to the Environmental Protection Agency (EPA) pursuant to Section 8(e) of the Toxic Substances Control Act. Under Tier 1 of VCCEP, hazard, exposure, risk, and data needs assessments are being developed for benzene in accordance with the VCCEP Federal Register notice (65 FR 81699-81718; December 26, 2000). This draft VCCEP children's risk assessment is preliminary and is intended to be submitted for review by an independent peer-review panel under the VCCEP process; this peer-review has not yet occurred. The Consortium has made no determination as to whether a significant risk of injury to health or the environment, as defined by TSCA Section 8 (e), is presented in the document.

The enclosed draft VCCEP children's risk assessment compares available exposure information on benzene from published sources to existing benzene guidance or safety values, from EPA and other recognized bodies, in order to develop quantified risk analyses. The Consortium has made no determination as to whether these draft analyses represent significant risk of injury to health or the environment as defined by TSCA Section 8(e).

The benzene Tier 1 VCCEP children's risk assessment will be submitted to the Agency, along with the entire Tier 1 VCCEP submission for benzene, as part of the VCCEP program.

If you have any questions, please contact me at (703) 741-5627 or via email at Andrew_Jaques@americanchemistry.com.

Sincerely yours,

Andrew M. Jaques

Andrew M. Jaques, Director
BTX VCCEP Consortium

Enclosure

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[1] BTX VCCEP Consortium members are BP, Chevron Phillips Chemical Company, The Dow Chemical Company, DuPont, Equistar, ExxonMobil Chemical Company, Flint Hills Resources, LP, Marathon Petroleum Company LLC, Shell Chemical LP, Sterling Chemical Company, Sunoco, Inc., TOTAL PETROCHEMICALS, USA, Inc.

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8.0 RISK ASSESSMENT

[by Sean Hays, Summit Toxicology; Colleen Cushing, Exponent]

In general, a risk assessment integrates findings of a hazard assessment and exposure assessment for a given chemical and provides a numerical, quantitative characterization of risk. This risk assessment was specifically designed to evaluate the potential for environmental exposure to benzene in the U.S. to result in adverse health effects in children, including prospective parents. It incorporates an analysis of the noncancer and cancer risks from benzene, including an evaluation of existing data on the likelihood that children will have an altered susceptibility or response to benzene-induced toxicity.

As the Exposure Assessment indicates (see Section 7), benzene is in the air in many environments where children are present, and it is also present in food, drinking water, and human milk (for nursing infants) at levels well below historical, and even more current, occupational levels. The U.S. Environmental Protection Agency (EPA), in its Integrated Risk Information System (IRIS) database (U.S. EPA, 2003) has established noncancer (last revised in 2003) and cancer risk levels (last revised in 2000) for benzene that were derived from human occupational epidemiology studies involving exposures that were many orders of magnitude higher than levels to which children are exposed in the U.S.

While the hazards identified from these studies are relevant for human risk assessment because they analyze human toxicological effects, the extrapolation of effect levels from these high-exposure studies to much lower environmental exposures presents challenges. In the IRIS database, EPA used linear default extrapolation methods, even though there is considerable data suggesting that benzene-induced cancer requires a sufficient threshold of exposure to pose a threat.

To evaluate the potential impact of EPA's assumptions regarding low-dose extrapolation of risk, this risk assessment compares the risks based on the EPA IRIS values and the risk based on a margin of safety (MOS) approach, using the same key studies and critical effects on which the IRIS values were developed to choose the points of departure (PODs). The risk assessment considers a margin of safety analysis for both cancer and noncancer effects.

8.1 Risk Assessment Approach

This risk assessment was conducted using two different approaches;

1) An EPA default (linear) type of risk assessment using the Reference Dose (RfD) and Cancer Slope Factor (CSF) to characterize risks.[1]

[1] Within the EPA default approach, a range of hazard quotients (HQ) are calculated using a range of RfCs/ RfDs. A range of RfCs/RfDs are employed to better characterize the debate about what constitutes a scientifically justified Reference Value (RV).

2) A Margin of Safety (MOS) approach that utilizes a point of departure (POD) to characterize risks.

Both cancer and noncancer risks to children and prospective parents are characterized based on the quantitative estimates of exposure presented in Section 7. Exposures from all background pathways of exposure, including inhalation, ingestion, and dermal contact, have been added together to determine a total average daily dose for each age bin. Additionally, exposures resulting from gasoline sources (i.e., refueling) have been aggregated with background exposures, and risks characterized. Estimates of potential risks for smokers and their children are made separately from benzene exposures derived from other background or source-specific sources. Comparing benzene exposures from smoking-derived sources with other sources provides important insights.

The exposure assessment provides estimates of typical and high-end exposures for almost every exposure scenario. For this risk assessment, aggregate exposures are calculated for the typical and high-end exposures by summing the respective typical and high-end exposure estimates from the inhalation, ingestion, and dermal pathways. This approach will undoubtedly yield some overly conservative results. In particular, aggregating for the "high end" will undoubtedly compound conservative assumptions and may over-estimate actual exposures that are likely to occur in the U.S. (even for the high-end). However, to the degree that exposures are dominated by one or a few exposure scenarios, this compounding issue becomes less critical.

The exposure assessment presented in this report suggests that indoor air (in the home) is the predominant pathway, and may contribute upward of 70%–80% of aggregate exposures for children in non-smoking households. For children in a smoking household, the background indoor air contributes approximately 50%–60% of total exposures, with exposures from environmental tobacco smoke (ETS) contributing approximately 20%–25% of total exposures. Therefore, the compounding of conservative estimates to develop an aggregate "high-end" exposure may be less significant than would be the case if all the exposure scenarios contributed equally to the aggregate exposures.

Indoor air levels of benzene in Alaskan homes are addressed as a separate exposure scenario. Age-specific risks are quantified using only the exposures from inhalation of indoor air in Alaskan homes. These risks are then compared to the risks calculated for typical and high-end continental U.S. home indoor air inhalation pathway.

For carcinogenic effects, exposures are calculated by averaging the total cumulative dose over a lifetime. The estimate of the average lifespan is assumed to be 70 years, based on EPA guidance (U.S. EPA 1991). The lifetime average daily dose is calculated as a time-weighted value over a 70-year lifespan using the average daily dose (ADD) and the applicable exposure duration for each age group.

$$\text{Lifetime Average Daily Dose} = \frac{(ADD_{<1yr} \times 1\ yr) + (ADD_{1\ to\ <2\ yr} \times 1\ yr) + (ADD_{2\ to\ <6\ yr} \times 4\ yr) + (ADD_{6\ to\ <16\ yr} \times 10\ yr) + (ADD_{16\ to\ <19\ yr} \times 3\ yr) + (ADD_{19\ to\ 70\ yr} \times 51\ yr)}{70\ years}$$

8.1.1 EPA Default Risk Assessment

Non-cancer:
EPA has developed equations to estimate potential risks of noncarcinogenic and carcinogenic health effects (U.S. EPA 1989). For noncarcinogenic health effects, a Hazard Quotient (HQ) is calculated, which is the ratio of the estimated exposure to the reference dose (RfD).

$$HQ = \frac{\text{Exposure (mg/kg-day)}}{\text{RfD (mg/kg-day)}}$$

For noncancer health effects, exposures are averaged over the duration of the exposure period and are expressed as the average daily dose (Table 7.53). All exposures quantified in the exposure assessment were calculated as absorbed doses. EPA's RfD is used in all HQ calculations, because it is an absorbed-dose based Reference Value (RV)[2].

Exposures resulting in an HQ that is less than 1 are unlikely to result in noncancer adverse health effects. As HQ values increase, the potential for toxicity increases. EPA states that the range of possible values around RfDs is "perhaps an order of magnitude" (Dourson 1993); therefore, the significance of intakes exceeding the RfD by one-half order of magnitude or less (i.e., HQs less than 5) must be considered carefully. As recommended by EPA guidance, all noncancer HQs and cancer risk estimates are expressed with one significant figure (U.S. EPA, 1989).

Cancer:
For carcinogenic endpoints, risk estimates are calculated by multiplying the exposure by the carcinogenic slope factor (CSF), expressed in $(mg/kg\text{-}day)^{-1}$.

$$\text{Risk} = \text{Exposure (mg/kg-day)} \times \text{CSF (mg/kg-day)}^{-1}$$

This yields a unitless estimate of risk, and should be interpreted as the probability of increased incidence of cancer in a lifetime. Therefore, a cancer risk estimate of 1×10^{-5} or 1×10^{-4} indicates a probability of 1 in 100,000 and 1 in 10,000, respectively, or 1 cancer in a population of 100,000 or 10,000 people, respectively, exposed to the levels used in the calculations.

8.1.1.1 Approach for Margin of Safety Assessment

EPA's Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005b) provides guidance for performing risk assessments on compounds that exhibit non-linear dose-response trends. According to the guidance, a Margin of Exposure (MOE) analysis

[2] EPA derived their RfD from the RfC by calculating the absorbed dose associated with the RfC:

$$\text{Reference Dose (absorbed)} = \frac{\text{Reference Concentration} \times \text{Inhalation Rate (10 m}^3\text{/day)} \times \text{Absorption Factor (50\%)}}{\text{Body Weight (70 kg)}}$$

should be conducted when the mode of action dictates a non-linear mechanism, yet not enough information and understanding of the biological processes exists to develop a validated biologically based dose-response model (Andersen et al., 2000; U.S. EPA, 2005b). The MOE approach provides some advantages, because "cancer slope factors derived from the linear option gives estimates of population risks that provide inappropriate risk-communication information to the public. The MOE does not provide an analysis as easily abused for estimating specific population risks" (Andersen et al., 2000).

There is a distinction between a margin of exposure (MOE) and margin of safety (MOS) assessment and in the way the MOS is being used in this risk assessment. The MOE approach uses a point of departure (POD) that represents a NOAEL or a "functional" threshold. The MOS, on the other hand, uses a POD that already contains some safety factors. This was also recognized by the European Union when they performed a MOS analysis and developed PODs that already contained safety factors for benzene[3] (ECB, 2003).

The MOS approach compares a calculated exposure to a point of departure (POD).

$$\text{MOS} = \frac{\text{POD (mg/kg-day)}}{\text{Exposure (mg/kg-day)}}$$

The MOS represents the ratio between the POD and the exposure dose. For example, an MOS of 100 indicates that the exposure is 100 times lower than the POD. An MOS of 1 would indicate that the estimated exposure equals the POD, and if the value is less than 1, the estimated exposures exceed the POD. Using this approach, larger MOSs indicate lower potential for risk. MOSs will be calculated both for cancer and noncancer health effects in this assessment. For noncancer health effects, exposures are expressed as the average daily dose (Table 7.53). For cancer, exposures are expressed as the lifetime average daily dose, as described above.

8.2 Toxicology Reference Values

The toxicology reference values used in this risk assessment for both the EPA default risk assessment approach (RfD and CSF) and in the MOS risk assessment approach (POD) are discussed below. Both the RfD and the CSF for benzene were derived from human occupational epidemiology studies. Since this risk assessment is designed to evaluate the risks to children, it must first be determined if kids are more sensitive than adults to the toxic effects of benzene and thus require some children's sensitivity adjustment factors to the current RfD, CSF, and any PODs established for this risk assessment. The following is an evaluation of the potential for children to be more sensitive to benzene's toxic effects. The findings from this evaluation help guide whether the toxicology reference values should be adjusted further to protect kids.

[3] The EU termed their POD a Critical Exposure Level (CEL). The CEL was derived by choosing a No Observed Adverse Effect Concentration (NOAEC) and then applying a "safety factor" which they termed a minimal MOS. The CEL was then used as the POD to calculate the Margins of Safety.

8.2.1 Potential for Increased Sensitivity of Benzene-Induced Hematopoietic Toxicity and AML in Children

The EPA's Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA 2005a) provides generic guidance that should be used in the absence of chemical specific information. There are no published data on the adverse effects of high-dose benzene exposure in children. Additionally, there is no reliable animal model for benzene-induced AML. Therefore, experimental studies using rodents cannot be used to address the issue of whether young animals are more sensitive than older animals to the leukemogenic effects of benzene.

Therefore, in the absence of benzene specific data, another known etiological agent for AML in children was used as a surrogate. Data that allowed for an evaluation of the effect of age on a child's risk of developing secondary leukemia was found in the cytotoxic chemotherapy literature. Several studies were located that reported treatment of different-aged children with the same disease with potentially leukemogenic drugs.

With cautious interpretation, studies describing therapy related or secondary AML (t-AML; treatment-induced AML) and hematopoietic toxicity (myelosuppression) in children following treatments with a variety of cancer therapeutic drugs may be a relevant surrogate to investigate age-related differences in susceptibility. This information is briefly described below and more fully in Addendum 8.A.

8.2.1.1 Children's Sensitivity Toward Treatment (Chemical)-Induced AML (t-AML)

Acute myelogenous leukemia (AML) has been positively linked to treatment with certain classes of cytotoxic chemotherapy. Drugs known to cause AML following chemotherapy of primary malignancy are usually alkylating agents or topoisomerase II inhibitors. Both children and adults can develop AML, yet rarely develop ALL, following treatment with these classes of anti-neoplastic drugs.

The first criterion that had to be evaluated to show that the chemotherapy-induced AML issue might be a reasonable surrogate for benzene-induced leukemia was to determine whether the secondary AML was a result of the chemotherapy treatments and not some other factor associated with the primary disease being treated or with some other component of the treatment (such as radiation). This could be proved by showing a clear dose-response between the relative risk (RR) of t-AML incidence and the dose of chemotherapy drugs. Many, if not all, of the studies evaluated for this project present data that clearly support a position that chemotherapy-induced leukemia in children (from both classes of leukemogenic therapies) follows a predictable dose response, with increasing risk associated with increasing cumulative doses (Deley et al., 2003; Tucker et al., 1987). Tucker et al. (1987) calculated an "alkylator score" based on the dose of the drugs used (Tucker et al., 1987) and showed a clear dose-response (Figure 8.1). A dose response for AML risk has also been reported for cycles of MOPP therapy, cumulative alkylating agent dose, and total cumulative dose of etoposide (Neglia et al., 2001; Deley et al., 2003; Meadows et al., 1989; Kaldor et al., 1990; Donaldson, 1993; van der Velden et al., 1988; Hawkings et al., 1992). As an example, Kaldor et al (1990) reported a dose response and risk of t-ANLL with cycles of MOPP. With 6 cycles, the relative risk of t-ANLL was reported to be 4.7, but with more than 6 cycles, the relative risk rose to 14 (Kaldor et al, 1990). Pedersen-Bjergaard et al, (1987) also reported a

dose-response relationship with increasing alkylating agents. Using dose metrics of low, medium, and high exposure, the risk of t-AML was 6.4, 11.3, and 37.5, respectively (Pedersen-Bjergaard et al., 1987).

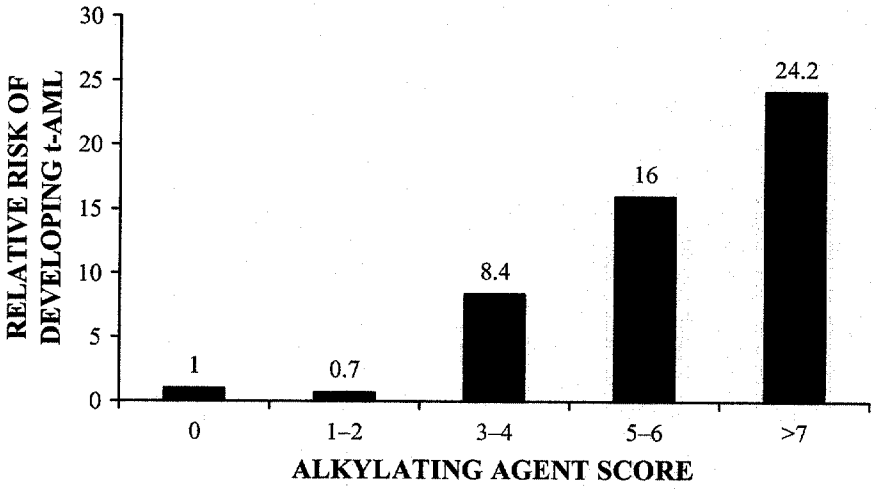

Figure 8.1: Relationship between RR of developing t-AML and the dose of the alkylating agent (represented by an "alkylating agent score"). Adapted from Tucker et al., (1987).

Next, the relationship between age and risk of developing t-AML following chemotherapy treatment was evaluated. A thorough review of the chemotherapy treatment literature indicated that there is no consistent evidence indicating younger children will be at increased risk; in fact, some studies indicate that younger children might actually have a decreased susceptibility (see Figure 8.2 and 8.3). Winick et al. (1993) reported the absolute risks of developing t-AML in children treated with etoposide for ALL. As can be seen in Figure 8.2, there was no age-related effect evident, with the exception that very young children (less than 3) had a slightly lower incidence rate of t-AML. Tucker et al. (1987) found that the absolute excess risk of t-AML following MOPP treatment rose progressively with the age of the patient (Figure 8.3). Similar results were found in numerous other studies. Addendum 8.A provides a thorough review of this information. The consistent finding throughout is that children do not appear to be more sensitive to chemotherapy-induced AML, and in some cases are reported to be less sensitive.

Furthermore, there is clear evidence in the published clinical literature that the effects of age on the risk of developing a secondary malignancy are highly dependent on the type of disease in question. As previously discussed, the risk of developing t-AML following chemotherapy does not appear to be related to the age of the patient. In contrast, the risk of developing various solid tumors is highly dependent on the age of the patient, with younger patients having a higher risk. Neglia et al (2001) reported that younger age correlated well with increased risk for solid tumors (CNS, breast, and thyroid) but not t-AML. An age dependency for risk of developing secondary solid tumors, but not secondary leukemia, in pediatric patients was also reported in a study by Loning et al (2001). Mauch and co-authors report that the risk for secondary breast cancer was highly age dependent and that young girls less than 15 had a much higher relative risk

(RR) and absolute excess risk (AER) than older girls and women (Mauch et al., 1996). This age dependency on risk was not observed with ANLL in this study (Mauch et al., 1996). Kuttesch et al (1996) demonstrated that age (3–40 years old) was not an independent risk factor for any secondary malignancies (including ANLL) following treatment of Ewing's Sarcoma.

These findings illustrate examples of studies with sufficient power that discern age-related differences, but did not find that the risk of AML was dependent on age. Currently available scientific and medical literature describing chemotherapy-induced AML in children appears to indicate that children are not more sensitive for developing AML following leukemogenic chemical exposure.

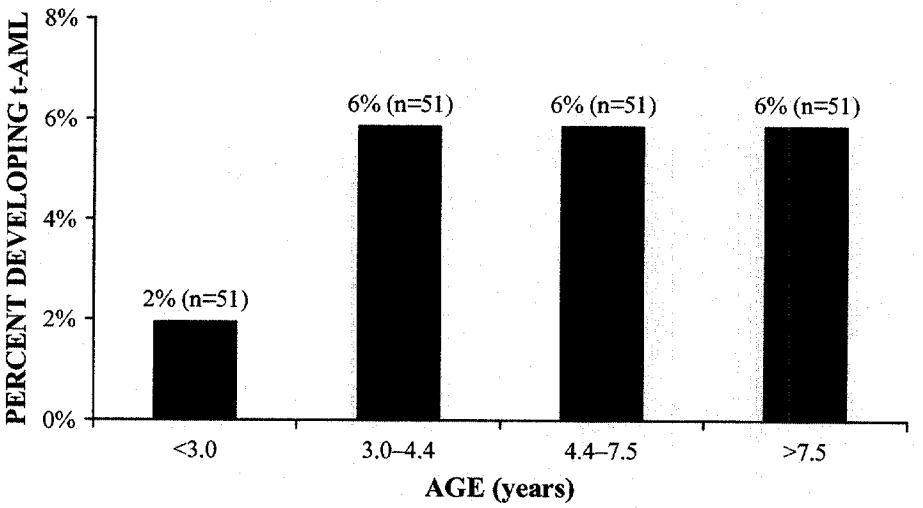

Figure 8.2: Percent of children who developed t-AML following treatment for ALL with etoposide (adapted from Winick et al., 1993).

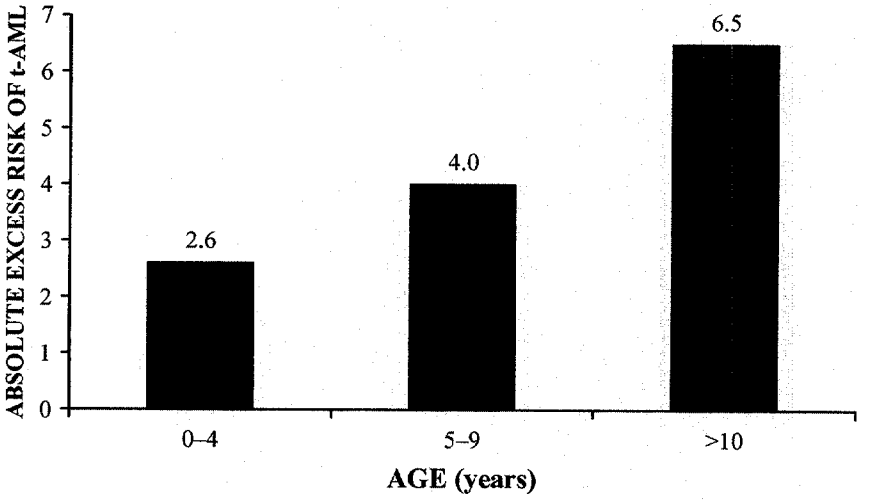

Figure 8.3: Age dependency of absolute excess risk of developing t-AML following treatment with alkylating agents. Adapted from Tucker et al. (1987)

8.2.1.2 Children's Sensitivity Toward Treatment (Chemical)-Induced Hematopoietic Toxicity

There are no available data to allow a direct comparison of benzene exposure required to result in hematopoietic toxicity between children and adults. However, limited data exist that do allow for an age-related comparison of bone marrow toxicity associated with exposure to various chemotherapeutic agents. Researchers from the National Cancer Institute (NCI) and associated institutions (Glaubiger et al., 1982; Marsoni et al., 1985) compared the maximum tolerated dose (MTD) for a variety of anti-neoplastic agents in children and adults (data obtained from various NCI sponsored clinical trials). Myelosuppression was the dose-limiting toxicity in both children and adults for 10 of the 17 drugs evaluated in this study. For 6 of the 10 drugs for which myelosuppression was the dose-limiting toxic effect in both populations, children had a higher MTD than adults. For the other four drugs, children had an equivalent MTD for three of the 17 drugs and a lower MTD in only one of the 17 drugs. The mean ratio of children/adult MTDs was 1.2. In addition, for every drug tested that had myelosuppression as the dose-limiting effect, the Phase II dose given to children was higher than that administered to adults on a mg/m^2 basis. Based on these results, investigators at NCI concluded that in the majority of cases, children are more resistant to the toxicity (myelosuppression) of anti-tumor drugs than adults (Glaubiger et al., 1982; Marsoni et al., 1985). This provided an independent line of evidence in support of the lack of an increased susceptibility in children to hematopoietic toxicity.

8.2.1.3 Children's Sensitivity Adjustment Factors

There is no consistent evidence in the published medical or scientific literature to support the hypothesis that children have an increased susceptibility to developing t-AML following chemical exposure. This was true for children treated with both classes of established leukemogenic drugs (alkylating agents and topoisomerase inhibitors).

These two drug classes are known to act through separate mechanisms; therefore, the lack of increased sensitivity for development of t-AML may be applicable to all chemical leukemogens. The available clinical literature also suggests that children are no more, and may be less, sensitive to chemical-induced hematopoetic toxicity following exposures to a range of chemotherapeutic drugs. While challenges and uncertainties exist in this comparison, the available published data appear to indicate that an age-related sensitivity difference to chemically induced leukemia and hematopoetic toxicity does not exist.

Based on these findings, there is no need to add additional children's sensitivity safety factors to any of the regulatory health guidance values (RfC or CSF) and the PODs for both noncancer and cancer.

8.2.2 Reference Values for EPA Default Risk Assessment

The following summarizes EPA's RfD/ RfC and CSFs for benzene.

8.2.2.1 Reference Concentration and Reference Dose

As discussed in Section 6.1, peripheral cytopenias are the most sensitive noncancer effect following exposures to high concentrations of benzene. Section 6.2.3 provides a thorough review of the literature on the subtle reproductive (fertility) and developmental effects associated with benzene exposures. It is clear from this review and from reviews conducted by other groups (ACGIH, 2001; ECB, 2003) that subtle reproductive and developmental effects either occur at maternally toxic doses or occur at exposures higher than those associated with cytopenias. Therefore, this risk assessment is conducted using health benchmarks based on the most sensitive noncancer endpoint, cytopenias. The decrease in absolute lymphocyte count (ALC) reported in Rothman et al. (1996) forms the basis of EPA's RfC and RfD (U.S. EPA, 2003). EPA derived an RfC of 3×10^{-2} mg/m^3 and an RfD of 4.0×10^{-3} mg/kg/day based on the same study and extrapolating based on total absorbed dose. There are several issues with how EPA derived their RfC and RfD that warrant discussion.

Problems with how EPA calculated the RfC and RfD

EPA used data from Rothman et al. (1996) to calculate both a reference concentration (RfC) for inhalation exposures and, by route-to-route extrapolation, a reference dose (RfD) for oral exposures (U.S. EPA 2003). The RfC and RfD were based on benchmark dose (BMD) modeling of the ALC data. Unlike the presence or absence of a tumor, ALC is a continuous endpoint; that is, there is a range of "normal" ALC values and thus no single clear definition for an adverse level. EPA selected as a default benchmark response (BMR) a one standard deviation change from the control mean. That is, an ALC would represent an adverse effect if it is more or less than one standard deviation from the mean of the control population. It should be noted that the range of ALCs reported by Rothman (even for the exposed workers) were all within the normal range of ALC values reported for adults. Therefore, while a dose-response was established, the ALCs for the workers from this cohort were all within the normal range of ALC values, despite having some extremely high exposures (in excess of 100 ppm TWA benzene concentration).

EPA's BMD modeling yielded a benchmark concentration (BMC) of 13.7 ppm (8-hr TWA), and a benchmark concentration lower limit (BMCL; 95% lower bound on the BMC) of 7.2 ppm (8-hr TWA). The BMCL was then converted from an occupational exposure (8-hr TWA, 5 days/wk) to a continuous exposure (24-hr/day, 7 day/wk), with a resulting value of 8.2 mg/m^3. The final step in the calculation of the RfC is the application of an uncertainty factor. The EPA applied an uncertainty factor (UF) of 300, which is a combination of four different values.

- **3**: for effect-level extrapolation, analogous to the UF used to extrapolate from a LOAEL to a NOAEL. EPA recognized that a decreased ALC "is not very serious in and of itself. Decreased ALC is a very sensitive sentinel effect that can be measured in the blood, but is not a frank effect, and there is no evidence that it is related to any functional impairment at levels of decrement near the benchmark response" (U.S. EPA, 2003).

- **10**: for intraspecies differences in response (human variability), intended to protect potentially sensitive human subpopulations.

- **3**: for subchronic to chronic extrapolation.

- **3**: for database deficiencies, because no two-generation reproductive and developmental toxicity studies for benzene were available.

That is, the UF = 3×10×3×3 = 270 (which was rounded by EPA to 300), would yield an RfC of 3.0×10^{-2} mg/m^3 ($8.2 / 270 = 2.7\times10^{-2}$ mg/m^3).

While considerable professional judgment and policy decisions go into the selection of UFs, these values are not beyond scientific debate. The following is a discussion of the issues surrounding EPA's choice of UFs used to derive the RfC/RfD for benzene and some suggestions for alternative UFs. The quantitative impact on the reference value of modifying the various UFs is summarized in Table 8.1.

- UF for effect level extrapolation: The effects reported in the cohort of workers studied by Rothman were still within the range of normal ALC, despite having some extremely high exposures to benzene (>100 ppm TWA for some workers). The selection of the POD to be one standard deviation from the control group is also a health protective (conservative) measure. EPA chose a value of 3, recognizing that the effects were not severe. EPA recognized that a decreased ALC "is not very serious in and of itself. Decreased ALC is a very sensitive sentinel effect that can be measured in the blood, but is not a frank effect, and there is no evidence that it is related to any functional impairment at levels of decrement near the benchmark response" (U.S. EPA, 2003). Had Rothman and coworkers performed their analysis using more exposure groups than just the < 31 ppm and > 31 ppm exposed groups, a NOAEL could likely have been identified and there would be no need for this adjustment factor. Despite this, it is most enlightening that all of the workers had ALCs within the normal range, despite some extremely high exposures. This, combined with the fact that the slight decrements in ALC is considered to be a very sensitive marker and is not,

according to EPA, related to any "frank effects", questions the scientific justification for EPA's use of a factor of 3 for an effect level extrapolation.

- UF for intraspecies sensitivity: Clinical data would suggest that children are not more sensitive than adults to the myelosuppressive effects of a variety of drugs, and in some cases may actually be less sensitive than adults. Therefore by analogy, children would not be expected to be more sensitive to the myelosuppressive or hematopoietic toxicity of benzene. Therefore, children do not appear to be one of the sensitive populations for benzene's toxic effects. Since the subject of this risk assessment is children, it would appear there is evidence to support that an UF of 3 (rather than 10) would be sufficiently protective.

- UF for subchronic to chronic adjustment: Evidence in humans and experimental animals indicates that cytopenias occur within weeks or months of exposure and upon removal from the environment or reduction in benzene concentration, alterations are likely to return to normal values (Green et al., 1981; Snyder et al., 1981). Rothman noted in their publication "Neither estimated cumulative life-time benzene exposure nor number of years worked in an exposed factory was significantly associated with any hematologic outcome" (Rothman et al., 1996). Therefore, there is no reason to suspect that the biological response from 6.3 years of exposure would be quantitatively or qualitatively different than that expected to occur following 7 years of exposure. This calls into question the biological rationale for EPA's subchronic to chronic uncertainty factor of 3. Therefore, this UF should not be used.

- UF for database deficiency: EPA determined that the absence of a two-generation reproductive study warrants an additional UF of 3. Benzene is arguably one of the most thoroughly studied chemicals regulated by EPA, with a vast number of studies having been conducted on the effects in exposed humans. The reproductive and developmental toxicology and epidemiology studies conducted for benzene were thoroughly reviewed in Section 6.2.3. From this review, it is clear that some rodent species are more sensitive than others (mice are more sensitive than rats) to the repro/developmental effects of benzene. It is unclear how results from sensitive rodent species would be applicable for predicting risks of repro/developmental effects in humans, thus a two-generation reproductive study may be uninformative for benzene. Therefore, this UF may be unwarranted.

Table 8.1 provides a summary of the RfCs and RfDs (absorbed dose) calculated using combinations of these alternate UFs. The range of RfDs (EPA's IRIS value as the low estimate and Alternative 3 as the high estimate) will be used in calculating HQs in this risk assessment (Table 8.2). Using a range of values for the RfC/RfD provides valuable information for risk managers. One of the shortcomings of a default risk assessment approach of using a single estimate of the RfC/RfD to calculate a HQ is that the uncertainty about the "safe" exposure level of a chemical is already built into the RfC/RfD and thus the risk calculation process. Therefore, risk managers are less informed of the uncertainty involved in the calculated risks unless a formal uncertainty analysis is conducted. For this risk assessment, a range of HQs were calculated using EPA's RfD as published in IRIS as well as an alternative RfD calculated using a modified set of uncertainty factors (Table 8.1 and 8.2). The resulting range of HQs provides a

better characterization of the range of estimated risks and highlights the regulatory, rather than scientific, uncertainty that is involved in using the EPA default risk assessment approach.

The HQs associated with occupational exposures are calculated using the ACGIH TLV (adjusted to an absorbed dose; ACGIH 2001). The ACGIH reviewed all of the literature and data on the carcinogenic and non-carcinogenic effects associated with benzene (including reproductive and developmental effects) and set their TLV at a level that would be health protective for cancer (the endpoint they deemed the most sensitive endpoint for benzene). Therefore, HQs less than 1.0 for occupational exposures should also indicate a lack of potential for reproductive and developmental effects.

8.2.2.2 Cancer Slope Factor

The literature on the leukemogenic potential of benzene in occupationally exposed workers has been thoroughly reviewed in Section 6.1. The literature demonstrates that benzene has been shown to cause AML in a small subset of highly exposed workers. Arguably the most important study of benzene and AML is the NIOSH sponsored retrospective cohort mortality study of workers involved with the manufacture of rubber hydrochloride (Pliofilm) at one of three plants in Ohio (Infante et al., 1977; Rinsky et al., 1981; Rinsky et al., 1987). EPA has derived a CSF based on this cohort.

The Rinksy et al. (1981, 1987) study analysis of the 'pliofilm' cohort was selected by the US EPA as the critical study for dose response analysis and for the quantitative estimation of cancer risk to humans (Rinsky et al., 1981, 1987). This study was selected because it has ample power, reasonably good estimates of exposure (except prior to 1946), a wide range of exposure from low to high levels and a relative lack of potential confounding chemicals. Further, the job activities of the various workers were fairly well documented. Based on data obtained from this cohort, the carcinogenic risk of inhaled benzene was calculated by Crump (1994). Crump presented 96 different unit risk calculations by considering different combinations of 1) disease endpoint, 2) additive or multiplicative models, 3) linear or non-linear exposure-response models, 4) exposure estimates for the Pliofilm cohort (Crump and Allen [1984] and Paustenbach et al. [1993]), and 5) cumulative or weighted exposure estimates (U.S. EPA, 2000). The unit risk estimates calculated by Crump (1996) span a factor of approximately 300 ranging from 8.6×10^{-5} to 2.5×10^{-2} at 1 ppm of benzene air concentration (U.S. EPA, 2000). EPA states that the risk estimates in the lower range correspond with the use of a sublinear exposure-response model and the risk estimates in the upper range correspond with the use of a linear exposure-response model.

EPA chose a narrow range of unit risk estimates of 7.1×10^{-3} to 2.5×10^{-2} at 1 ppm (only a factor of approximately 3 between these values) for their IRIS values (U.S. EPA, 2000). EPA states that this conservative range of cancer unit risk estimates was selected because "the shape of the exposure dose-response curve cannot be considered without a better understanding of the biological mechanism(s) of benzene induced leukemia" (U.S. EPA, 2000). Therefore, it was a policy decision to choose a narrow range of the most conservative unit risk estimates calculated by Crump (1996).

Using only the narrow range of CSFs chosen by EPA provides a narrower range of risk estimates, implying less uncertainty. However, using only the narrow range of CSFs

chosen by EPA actually conveys a false sense of certainty about risk estimates for children exposed to benzene. Therefore, for the purposes of this risk assessment, cancer risk estimates are calculated using the range of CSFs chosen by EPA (U.S. EPA, 2000) and by using the lower bound on the values calculated by Crump (1996) as reported by EPA (U.S. EPA, 2000). Using a range of CSFs that span the broader range of risk estimates calculated by Crump from the Pliofilm cohort provides a better perspective on the range of risk estimates that could be derived using the Pliofilm cohort, but yet still using a dose-response model to calculate risks below the exposures encountered by the Pliofilm cohort.

Table 8.2 provides details on how the CSFs were calculated. The quantitative oral unit risk estimate is an extrapolation from the known inhalation dose-response to the potential oral route of exposure. The inhalation unit risk range is converted to an absorbed-dose slope factor, which is expressed in units of risk per mg/kg-day. The inhalation to absorbed-dose conversion assumes a standard air intake of 20 m^3/day, a standard body weight of 70 kg for an adult human and 50% inhalation absorption.

The CSFs used in the risk assessment are (Table 8.2):
Upper-bound linear model = 5.5×10^{-2} $(mg/kg/day)^{-1}$
Lower-bound linear model = 1.5×10^{-2} $(mg/kg/day)^{-1}$
Lower-bound nonlinear model = 1.9×10^{-4} $(mg/kg/day)^{-1}$

8.2.3 Points of Departure for Margin of Safety Assessment

The following is a summary of the PODs chosen for this MOS risk assessment. The PODs chosen for this risk assessment are values that have already been established by regulatory agencies and scientific organizations and established as "safe" exposure limits. Therefore, the PODs summarized below already contain some measures of safety built into them. Based on our current understanding of the science (see Section 6.1), the "functional" thresholds for both cancer and noncancer effects would undoubtedly be higher than the PODs used in this risk assessment.

8.2.3.1 Point of Departure for Non-Cancer Effects

The European Union (EU) recently conducted a risk assessment for occupational and environmental exposures to benzene (ECB, 2003). The EU performed their risk assessment by employing a Margin of Safety (MOS) analysis which is identical to the MOS approach described above. The MOS analysis conducted by EU scientists was based on deriving a "threshold" effect level for noncancer hematopoietic toxicity to compare with quantified exposures estimates. The Critical Exposure Level (CEL), as calculated by the EU is essentially a "threshold", a level of exposure below which no adverse effect would be predicted to occur. The CEL was derived by first choosing a No Observed Adverse Effect Concentration (NOAEC). The EU calculated their CEL by dividing the NOAEC by a "minimal MOS" (which serves essentially the same purpose as EPA's uncertainty factors). The EU derived a CEL for a variety of endpoints, including cancer.

For their repeated dose toxicity, the EU used the Rothman et al. (1996) study as the critical study and they derived a NOAEC of 1 ppm. They considered this an effective

threshold for reductions in ALC and used a minimal MOS of 1. They therefore derived a CEL of 1 ppm or 3.2 mg/m^3. Converting this to an absorbed dose yields a POD of 0.5 mg/kg/day. This value will be used as the POD for the noncancer MOS calculations (Table 8.3).

8.2.3.2 Point of Departure for Cancer

As described in Section 6.1, a functional threshold for the induction of benzene-induced AML is supported by the available epidemiological data. Multiple epidemiological studies from the 1930s through the 1980s strongly support the hypothesis that a threshold exists for benzene's hematopoietic toxicity, including the risk for developing AML. The EPA cancer slope factor is based on the Rinsky et al. (1987) study. There have been four exposure analyses of this cohort (Rinsky et al. 1987; Crump and Allen 1984; Paustenbach et al. 1992; Williams and Paustenbach, 2003), and although they differ with regard to methodologies and conclusions, none has reported an excess leukemia risk below 40 ppm-yrs, with an average value of ~200 ppm-years (Paustenbach et al., 1992; Rushton et al., 1997; Paxton et al., 1994; Wong, 1995; Aksoy, 1980). Other authors believe that the threshold could be much higher and that, based on exposure estimates from Crump and Allen and Paustenbach, the AML threshold would correspond to 370 or 530 ppm-yrs, respectively (Crump and Allen, 1984; Paustenbach et al., 1992; Wong, 1995). An analysis published by Glass et al. (2003) reports an increased ANLL[4] risk at lower levels of cumulative benzene exposures (> 8 ppm-years) than previously reported, but still appear to have found a functional threshold in their cohort[5] (Glass et al., 2003). The vast majority of the existing epidemiology evidence on the relationship between benzene and AML supports the existence of a threshold for this effect.

While the actual exposure/dose required for AML is not universally agreed upon, the existence of a threshold for AML is consistent with epidemiological data, as well as clinical data obtained from secondary leukemia arising from ionizing radiation and/or chemotherapy and the current understanding of bone marrow patho-physiology and biology. Emerging evidence in the biological mechanism of benzene-induced AML suggests that benzene and/or its metabolites may induce AML via toxic disruption of the regulatory mechanism of cell growth and differentiation (Irons and Stillman, 1993; Irons et al., 1992; Snyder and Kalf, 1994). Further, benzene metabolism has been determined to follow non-linear Michaelis-Menton kinetics (Travis et al., 1990). Given the non-linear nature of benzene metabolism, the use of a linear model for excess cancer risk calculations will likely overestimate the risk, particularly at low exposure levels (ACGIH, 2001). These observations provide a biological basis for the observed threshold evident in epidemiological data (Wong and Raabe, 1995; World Health Organization, 1993; ACGIH, 2001).

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[4] Glass et al. (2003) used the term ANLL (acute non-lymphocytic leukemia) because they included two leukemia cases that were not classified as AML, but were thought to be closely related.

[5] Some methodological problems decrease the potential usefulness of this study for risk assessment purposes. Some investigators believe that the expected cases of ANLL in the baseline or control group in this study were under-represented. This would change the calculated risks, as well as the interpretation of this data, particularly at low exposures (Schnatter, 2004; Goldstein, 2004). There are also problems with case selection and controlling for various types of bias (Schnatter, 2004; Goldstein, 2004).

The scientific literature is consistent in its demonstration that refinery workers do not have an elevated risk of developing AML, and indicates that a threshold exists for AML induction by benzene exposure (Theriault and Goulet, 1979; Naumann et al., 1993; Raabe et al., 1998; Marsh et al., 1991; Wong et al., 1986; Dagg et al., 1992; Satin et al., 1996; Thomas et al., 1982; Austin et al., 1986; Divine et al., 1987; Austin and Schnatter, 1983). The literature also suggests that auto or truck mechanics do not have an elevated risk of developing AML (Hotz and Lauwerys, 1997; Jarvisalo et al., 1984; Linos et al., 1980; Linet, 1988; Howe and Lindsay, 1983; Jacobs et al., 1993; Giles et al., 1984; Mele et al., 1994).

The ACGIH evaluated all of the potential toxic effects of benzene in humans and chose the AML incidence data from the 'pliofilm' cohort to derive a TLV-TWA for benzene of 0.5 ppm[6]. Prior to 1997, the TLV was 10 ppm, and even greater in years prior to 1976 (ACGIH, 2001).

The current TLV of 0.5 ppm will be used in this assessment as the POD for the occupationally exposed scenarios (ACGIH, 2001). Since the TLV is a workplace standard, the TLV is multiplied by 10 m^3/20 m^3 (this is typically used in lieu of the older 8/24 – as was done by EPA in deriving their RfC for benzene - scaling factor to adjust for the proportion of air inhaled during a workday versus an entire day) and 5/7 to convert it to a continuous exposure applicable for the general population exposure scenarios. This yields a POD for cancer effects of 0.18 ppm or 0.57 mg/m^3 for the general population (continuous exposures). This value is similar to the EU's calculated Critical Exposure Llevel (CEL) for their cancer risk assessment of 0.1 ppm. The EU derived their CEL by choosing 1 ppm as their "starting point" and applied a minimal margin of safety (MOS) of 10 to yield a CEL of 0.1 ppm (1 ppm / 10 = 0.1 ppm) (ECB, 2003).

Both the TLV and the TLV adjusted value are converted to an inhaled dose (Table 8.3). The resulting inhaled dose based PODs are;
Occupational POD: 0.1 mg/kg/day
General population POD: 0.08 mg/kg/day

8.3 Results

8.3.1 EPA Default Risk Assessment Approach

The results of the noncancer risk calculations are provided in Tables 8.4 (for children's exposures) and 8.5 (for adults' exposures). High and low HQs are provided for each exposure scenario and corresponding age group. The high risk estimate was based on EPA's RfD (adjusted to absorbed dose). The low risk estimate is calculated by dividing exposures by Alternative 3 RfD listed in Table 8.1. This higher RfD yields lower estimated risks and is provided to highlight the uncertainty about the RfD and estimated noncancer risks from benzene exposures.

Using the EPA IRIS RfD, HQs of 1 were calculated for children < 1 year old and 1 to <2 years of age exposed to high-end background sources of benzene (all routes

[6] The Glass et al. (2003) study had not been published when the ACGIH developed their most recent TLV.

aggregated) and for adolescents and adults who smoke cigarettes. Using the Alternative 3 RfD, no exposure scenarios exceed an HQ of 1. HQs for an infant ingesting human milk from an occupationally exposed mother were the same as HQs for a nursing infant whose mother was not occupationally exposed.

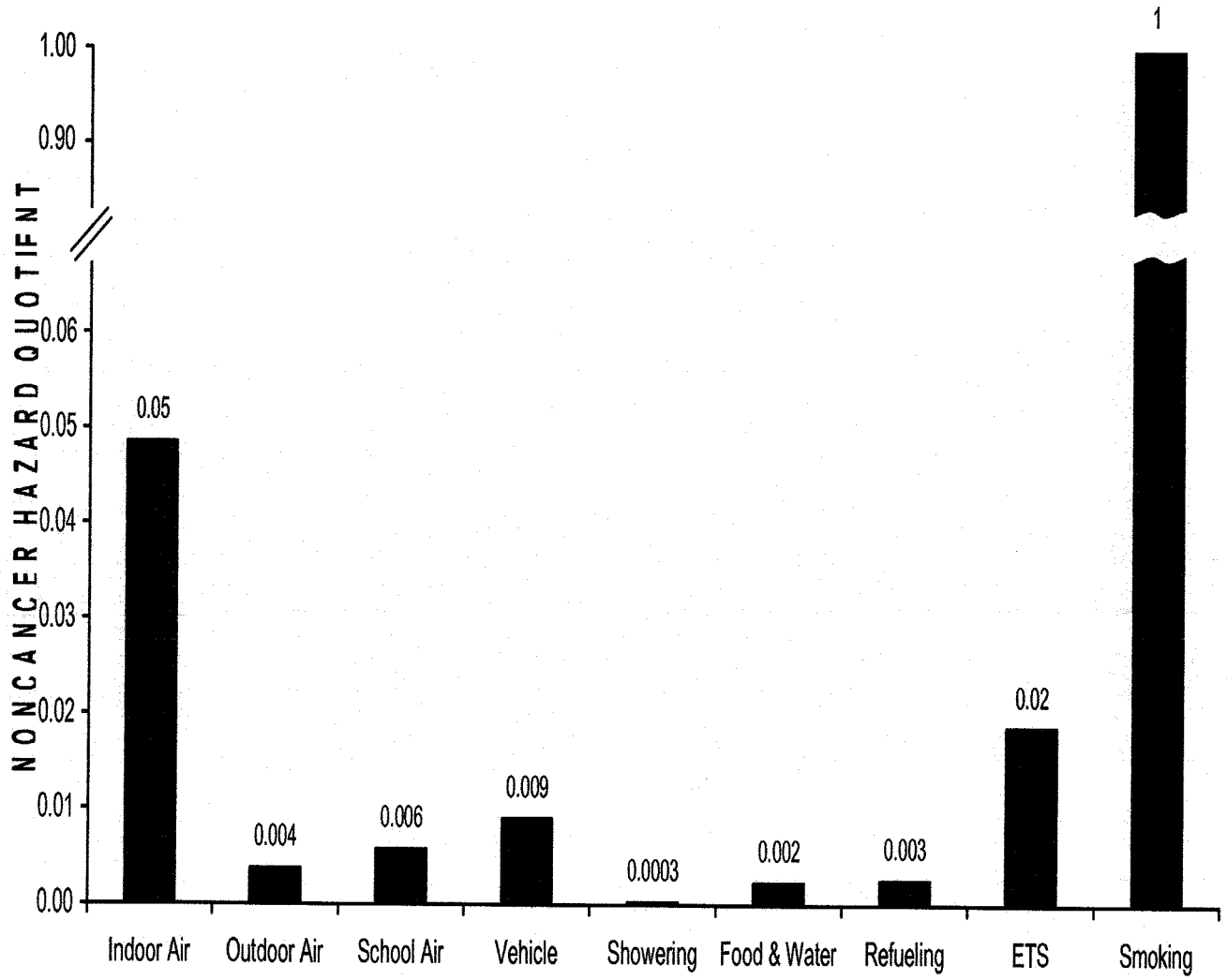
Cancer risks were calculated using the range of CSFs provided by U.S. EPA (2003) and using the lower bound on the CSF calculated by Crump (1994) as reported by U.S. EPA (2003). Table 8.6 provides potential excess risk estimates for males and females based on lifetime average daily doses. Using the upper-bound linear model CSF, background aggregated exposures (from urban and rural, typical and high end) are predicted to be associated with excess cancer risks greater than 1×10^{-5}. Using the lower-bound linear model CSF, background aggregated exposures (from urban and rural, typical and high end) are predicted to be associated with excess cancer risks less than 1×10^{-6}. Only smoking tobacco (direct mainstream smoking) leads to predicted excess cancer risks greater than 1×10^{-4}.

Table 8-7 provides both HQs and potential excess cancer risk estimates from indoor air (in-home), comparing the typical and high end estimates from the Continental U.S. and the exposure from Alaskan homes. As was discussed in Section 7.2.1.5, concentrations of benzene in Alaskan homes with attached garages are significantly higher than concentrations of benzene in homes in the continental U.S. The resulting HQs for children living in Alaskan homes with attached garages varies considerably. The HQ for the <1 year old ranges from 0.2 (low HQ estimate using Alternative 3 RfD) to 5.0 (using EPA's RfD from IRIS). Using EPA's RfD, the only age group that has an HQ lower than 1 is the 16 to <19 year old age group. Using the Alternative 3 RfD, all HQs are below 1 for both Alaska and the continental U.S. Estimated potential excess cancer risks exceed 1×10^{-4} for Alaskans using the upper-bound linear model CSF and are predicted to be 1×10^{-6} using the lower-bound nonlinear model CSF. Table 8.8 provides a comparison of HQs for adults exposed to indoor air from homes in the Continental U.S. (typical and high end) and Alaskan homes. HQs exceed 1 using EPA's RfD and are significantly less than 1 using Alternative 3 RfD.

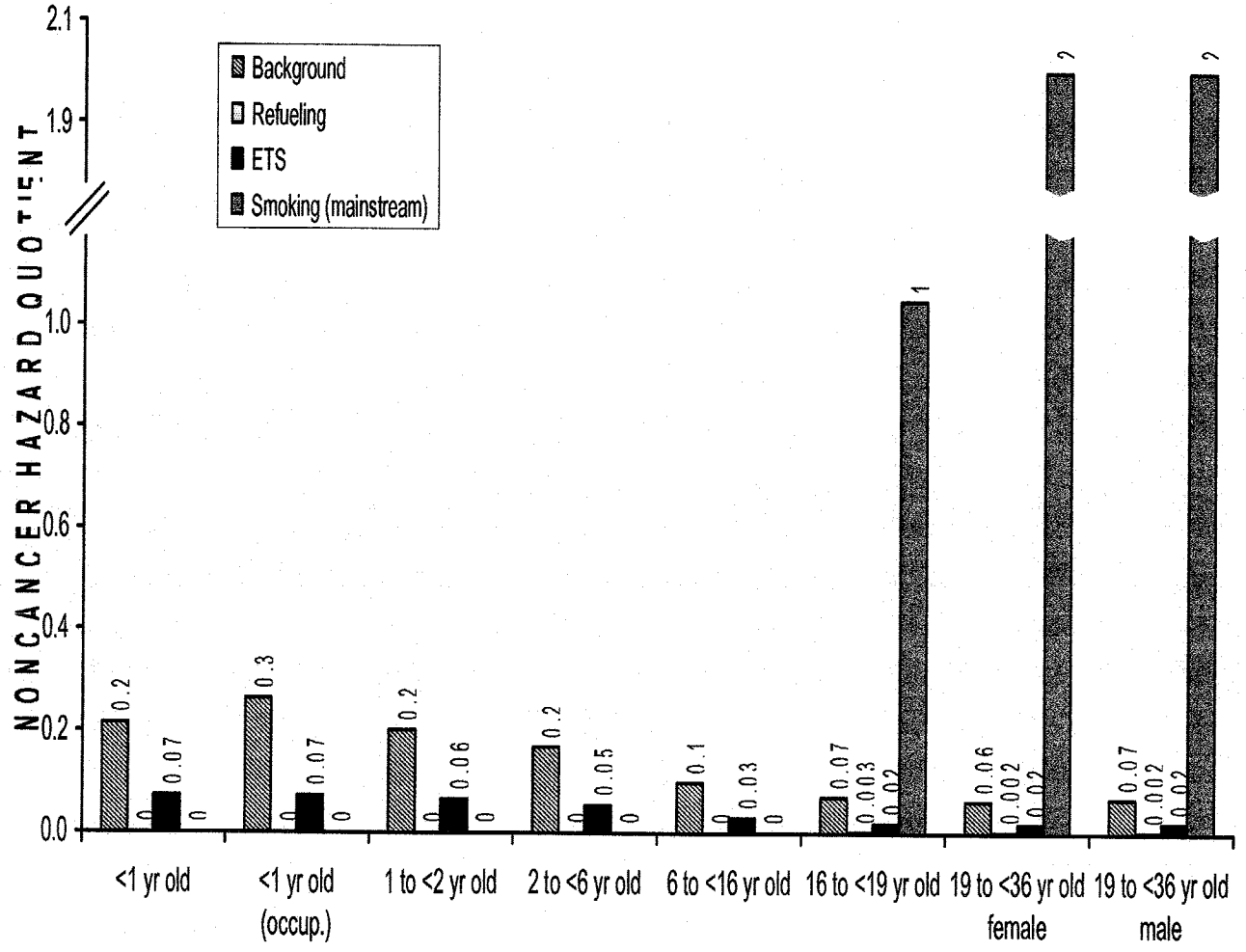
Figures 8.4 and 8.5 provide insight on the exposure scenarios that contributed most to the overall exposures and HQs for the 'typical' exposures. Figure 8-4 shows the relative contribution of the individual exposure scenarios for a 16 to 19 year old adolescent. As can be seen, smoking is the predominant contributor to overall benzene exposures and HQs when the adolescent smokes. Because of the limited durations and frequency with refueling a car and riding in a car, these exposure sources provide little towards a child's aggregate exposures and HQ. Indoor air contributes the largest fraction of the remaining sources towards benzene exposures and HQs, with ETS providing the second most significant exposure source. Figure 8.5 provides estimates of the HQ for all age groups comparing aggregated background sources to the HQs from ETS, refueling a car and from active smoking in adolescents and adults. As can be seen, the HQ associated with active smoking is significantly greater than all other exposures combined. These figures illustrate the fact that smoking is the dominant source of benzene exposures and thus HQ and potential health risks from benzene exposures.

8.3.2 Margin of Safety Analysis

Table 8.9 provides estimates of the MOSs for noncancer effects for the different exposure scenarios/sources and for aggregated exposures for each age group. For aggregate exposures, the MOSs range from approximately 100 to 2,100. The MOS for smoking is estimated to range from approximately 50 to 100. Table 8.10 provides estimates of the MOSs for noncancer effects in adults. Tables 8.11 and 8.12 provide MOS estimates for children and adults, respectively, associated with in-home inhalation exposures from living in homes in the continental U.S. and Alaskan homes with attached garages. Table 8.13 provides estimates of the MOSs for cancer. The MOS for lifetime average daily doses for males and females are provided for each exposure source and for aggregate exposures. The cancer MOSs for aggregate exposures for all background sources of exposure range from approximately 50 to 250. The MOS for smoking is estimated at approximately 10. Table 8.14 compares the MOSs for cancer associated with lifetime average in-home inhalation exposures from living in Continental U.S. homes and Alaskan homes with attached garages. The predicted MOSs associated with in-home inhalation exposures for children living in Alaskan homes with attached garages ranges from 25 to 150 for noncancer effects (Table 8.11) and are above 10 for cancer (Table 8.14).



Notes: Hazard quotients were calculated using the default IRIS reference dose.
Typical values were used for all pathways and outdoor air is urban.



Notes: Hazard quotients were calculated using the default IRIS reference dose.
Typical values were used for all pathways and outdoor air is urban.

Table 8.1. Derivation of noncancer references values for benzene

Calculation of absorbed-dose noncancer reference values for benzene based on Rothman et al. 1996. Table demonstrates the quantitative impact of selecting different uncertainty and modifying factors.

	Units	Uncertainty Factor Category			
		IRIS Value	Alternative 1	Alternative 2	Alternative 3
Bench Mark Concentration Lower Limit (BMCL)	ppm	7.2	7.2	7.2	7.2
Adjusted from workplace to general population					
From 5 to 7 days/week exposure frequency (5/7)		0.714	0.714	0.714	0.714
From 10 to 20 m^3/day inhalation rate (10/20)		0.5	0.5	0.5	0.5
BMCL - general population	ppm	2.57	2.57	2.57	2.57
Convert units from ppm to mg/m^3					
M.W./24.45 (78.11/24.45)		3.19	3.19	3.19	3.19
BMCL - general population	mg/m^3	8.20	8.20	8.20	8.20
Uncertainty and Modifying Factors					
Effect level extrapolation		3	3	3	3
Intraspecies variability		10	3	3	3
Subchronic to chronic		3	3	1	1
Database deficiency		3	3	3	1
Composite UF		300 [a]	81	27	9
RfC (Reference Concentration): BMCL-general pop./Composite UF	mg/m^3	**0.027**	**0.10**	**0.30**	**0.91**
Converted from concentration to absorbed dose					
Inhalation rate	m^3/day	20	20	20	20
Absorption factor	%	50%	50%	50%	50%
Body weight (kg)	kg	70	70	70	70
RfD (Reference dose, absorbed)	mg/kg-day	0.004	0.01	0.04	0.1

Table 8.2. Toxicity values for benzene: EPA default approach

Calculation of absorbed-dose noncancer reference values and cancer slope factors for benzene. Table demonstrates the range of values obtained from various assumptions and modeling approaches.

		Noncancer Reference Values			Cancer Slope Factors		
	Unit	IRIS default	Alternative 3[a]	TLV-Based[b]	Lower-Bound Nonlinear Model	Lower-Bound Linear Model	Upper-Bound Linear Model
Initial value (air concentration)	ppm	--	--	0.5	--	--	--
Initial value (air unit risk)	ppm^{-1}	--	--	--	8.6E-05		
Conversion factor 1	mg/m^3 per ppm	--	--	3.19	3.19	--	--
Initial value (air concentration)	mg/m^3	0.03	0.9	1.6	--	--	--
Initial value (air unit risk)	$(\mu g/m^3)^{-1}$	--	--	--	2.7E-08	2.2E-06	7.8E-06
Conversion factor 2	µg/mg	--	--	--	1,000	1,000	1,000
Inhalation rate	m^3/day	20	20	10	20	20	20
Absorption factor	%	50%	50%	50%	50%	50%	50%
Body weight	kg	70	70	70	70	70	70
Reference Dose [RfD] (absorbed)	**mg/kg-day**	**0.004**	**0.1**	**0.1**	**--**	**--**	**--**
Cancer Slope Factor [CSF] (absorbed)	**$(mg/kg\text{-}day)^{-1}$**	**--**	**--**	**--**	**1.9E-04**	**1.5E-02**	**5.5E-02**

Note: Because both the reference dose and the cancer slope factor were calculated on an absorbed-dose basis, the same value is used for all pathways (inhalation, ingestion, and dermal).

[a] See Table 8-1 and text for details.

[b] Value for adult occupational exposures, based on the ACGIH threshold limit value (TLV).

$$\text{Reference Dose (absorbed)} = \frac{\text{Initial Value} \times \text{Inhalation Rate} \times \text{Absorption Factor}}{\text{Body Weight}}$$

Table 8.3. Points of departure for margin of safety approach
Calculation of absorbed-dose points of departure (POD) for benzene.

	Unit	Cancer General Population	Noncancer General Population
Initial value (based on workplace exposure)	ppm	0.5	--
Initial value (based on general population exposure)	ppm	--	1
Adjusted from workplace to general population			
From 5 to 7 days/week exposure frequency (5/7)	days/days	0.714	--
From 10 to 20 m^3/day inhalation rate (10/20)	m^3/day / m^3/day	0.5	--
Initial value - general population	ppm	0.179	--
Conversion factor 1	mg/m^3 per ppm	3.19	3.19
Inhalation rate	m^3/day	20	20
Absorption factor	%	50%	50%
Body weight	kg	70	70
Point of departure	**mg/kg-day**	**0.08**	**0.5**

Note: Because all points of departure are calculated on an absorbed-dose basis, the same value is used for all pathways (inhalation, ingestion, and dermal).

$$\text{Initial value (general population)} = \text{Initial Value}_{\text{workplace}} \times \frac{5 \text{ days}}{7 \text{ days}} \times \frac{10 \text{ m}^3\text{/day}}{20 \text{ m}^3\text{/day}}$$

$$\text{Point of departure} = \frac{\text{Initial Value}_{\text{gen. pop.}} \times \text{Conversion Factor 1} \times \text{Inhalation Rate} \times \text{Absorption Factor}}{\text{Body Weight}}$$

Table 8.4. Noncancer hazard quotients associated with benzene exposures

Results of noncancer risk calculations. High and low hazard quotients are provided for each exposure scenario and corresponding age group for children.

	Noncancer Hazard Quotient (unitless)[a]					
	<1 yr old		<1 yr old (occup.)[b]		1 to <2 yr old	
	Low	High	Low	High	Low	High
INHALATION PATHWAYS						
Outdoor air (ambient, total)						
Rural - Typical	0.0001	0.003	0.0001	0.003	0.00009	0.002
Rural - High End	0.0002	0.005	0.0002	0.005	0.0001	0.003
Urban - Typical	0.0003	0.007	0.0003	0.007	0.0002	0.005
Urban - High End	0.0008	0.02	0.0008	0.02	0.0006	0.01
Indoor air (in-home, total)						
Typical	0.007	0.2	0.007	0.2	0.006	0.2
High End	0.03	0.8	0.03	0.8	0.03	0.7
In school						
Typical	--	--	--	--	0.0002	0.004
High End	--	--	--	--	0.0008	0.02
In vehicle - typical	0.0009	0.02	0.0009	0.02	0.0008	0.02
Showering						
Typical	0	0	0	0	0.0002	0.006
High End	0.002	0.04	0.002	0.04	0.005	0.1
BACKGROUND (summed by pathway)						
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)						
Rural - Typical	0.008	0.2	0.008	0.2	0.008	0.2
Rural - High End	0.04	0.9	0.04	0.9	0.04	0.9
Urban - Typical	0.008	0.2	0.008	0.2	0.008	0.2
Urban - High End	0.04	0.9	0.04	0.9	0.04	0.9
Ingestion Pathway (food & water)						
Typical	0.0004	0.009	0.002	0.06	0.0004	0.01
High End	0.008	0.2	0.01	0.4	0.006	0.1
Dermal Pathway (showering)						
Typical	0	0	0	0	9.0E-06	0.0002
High End	0.00002	0.0005	0.00002	0.0005	0.00002	0.0006
BACKGROUND (all pathways)						
Rural - Typical	0.008	0.2	0.01	0.3	0.008	0.2
Rural - High End	0.04	1	0.05	1	0.04	1
Urban - Typical	0.009	0.2	0.01	0.3	0.008	0.2
Urban - High End	0.04	1	0.05	1	0.04	1
SOURCE-SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	0.003	0.07	0.003	0.07	0.003	0.06
Mainstream (smoker's dose)	--	--	--	--	--	--
Refueling						
Typical	--	--	--	--	--	--
High End	--	--	--	--	--	--
Occupational						
Typical	--	--	--	--	--	--
High End	--	--	--	--	--	--
BACKGROUND PLUS REFUELING						
Rural - Typical	0.008	0.2	0.008	0.2	0.008	0.2
Rural - High End	0.04	1	0.04	1	0.04	1
Urban - Typical	0.009	0.2	0.009	0.2	0.008	0.2
Urban - High End	0.04	1	0.04	1	0.04	1

Table 8.4. (cont.)

	Noncancer Hazard Quotient (unitless)[a]					
	2 to <6 yr old		6 to <16 yr old		16 to <19 yr old	
	Low	High	Low	High	Low	High
INHALATION PATHWAYS						
Outdoor air (ambient, total)						
Rural - Typical	0.0002	0.006	0.00009	0.002	0.00007	0.002
Rural - High End	0.0003	0.008	0.0001	0.003	0.00009	0.002
Urban - Typical	0.0005	0.01	0.0002	0.005	0.0001	0.004
Urban - High End	0.001	0.03	0.0005	0.01	0.0004	0.01
Indoor air (in-home, total)						
Typical	0.005	0.1	0.003	0.07	0.002	0.05
High End	0.02	0.5	0.01	0.3	0.009	0.2
In school						
Typical	0.0002	0.006	0.0003	0.008	0.0002	0.006
High End	0.001	0.03	0.001	0.04	0.001	0.03
In vehicle - typical	0.0008	0.02	0.0005	0.01	0.0004	0.009
Showering						
Typical	0.00007	0.002	0.00001	0.0004	0.00001	0.0003
High End	0.001	0.03	0.0003	0.007	0.0002	0.005
BACKGROUND (summed by pathway)						
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)						
Rural - Typical	0.006	0.2	0.004	0.09	0.003	0.07
Rural - High End	0.03	0.6	0.02	0.4	0.01	0.3
Urban - Typical	0.006	0.2	0.004	0.09	0.003	0.07
Urban - High End	0.03	0.7	0.02	0.4	0.01	0.3
Ingestion Pathway (food & water)						
Typical	0.0004	0.01	0.0002	0.004	0.00009	0.002
High End	0.004	0.1	0.002	0.05	0.001	0.03
Dermal Pathway (showering)						
Typical	9.0E-06	0.0002	6.0E-06	0.0002	5.0E-06	0.0001
High End	0.00002	0.0006	0.00002	0.0004	0.00001	0.0004
BACKGROUND (all pathways)						
Rural - Typical	0.006	0.2	0.004	0.1	0.003	0.07
Rural - High End	0.03	0.7	0.02	0.4	0.01	0.3
Urban - Typical	0.007	0.2	0.004	0.1	0.003	0.07
Urban - High End	0.03	0.8	0.02	0.4	0.01	0.3
SOURCE-SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	0.002	0.05	0.001	0.03	0.0007	0.02
Mainstream (smoker's dose)	--	--	--	--	0.04	1
Refueling						
Typical	--	--	--	--	0.0001	0.003
High End	--	--	--	--	0.001	0.03
Occupational						
Typical	--	--	--	--	--	--
High End	--	--	--	--	--	--
BACKGROUND PLUS REFUELING						
Rural - Typical	0.006	0.2	0.004	0.1	0.003	0.07
Rural - High End	0.03	0.7	0.02	0.4	0.01	0.3
Urban - Typical	0.007	0.2	0.004	0.1	0.003	0.07
Urban - High End	0.03	0.8	0.02	0.4	0.01	0.3

(footnotes on following page)

Table 8.4. (cont.)

Notes:

-- – No value calculated because no benzene exposures are applicable to this category for this age group.
Hazard quotient [HQ] = Average Daily Dose / Reference Dose
Average daily doses are summarized in Table 7.53.
Reference doses used for calculations in this table are presented in Table 8.2.
ETS – environmental tobacco smoke

[a] Noncancer hazard quotients are calculated using the IRIS RfD (labeled High) and Alternative 3 RfD (labeled Low). See Tables 8.1,8.2, and text.

[b] Values represent hazard quotients associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

[c] Value is calculated using the occupational threshold limit value (TLV) instead of a reference dose. See Table 8.2 and text for details.

Table 8.5. Noncancer hazard quotients associated with benzene exposures—adults

Results of noncancer risk calculations. High and low hazard quotients are provided for each exposure scenario for adults.

	Noncancer Hazard Quotient (unitless)[a]			
	19 to <36 yr old female		19 to <36 yr old male	
	Low	High	Low	High
INHALATION PATHWAYS				
Outdoor air (ambient, total)				
Rural - Typical	0.00004	0.001	0.00004	0.001
Rural - High End	0.00006	0.001	0.00006	0.002
Urban - Typical	0.00009	0.002	0.0001	0.002
Urban - High End	0.0002	0.006	0.0003	0.007
Indoor air (in-home, total)				
Typical	0.002	0.05	0.002	0.05
High End	0.009	0.2	0.01	0.3
In school				
Typical	--	--	--	--
High End	--	--	--	--
In vehicle - typical	0.0003	0.007	0.0003	0.008
Showering				
Typical	6.0E-06	0.0001	6.0E-06	0.0001
High End	0.0001	0.003	0.0001	0.003
BACKGROUND (summed by pathway)				
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)				
Rural - Typical	0.002	0.06	0.003	0.06
Rural - High End	0.01	0.2	0.01	0.3
Urban - Typical	0.002	0.06	0.003	0.06
Urban - High End	0.01	0.2	0.01	0.3
Ingestion Pathway (food & water)				
Typical	0.0001	0.003	0.0001	0.003
High End	0.001	0.03	0.001	0.03
Dermal Pathway (showering)				
Typical	4.0E-06	0.0001	4.0E-06	0.0001
High End	0.00001	0.0003	0.00001	0.0003
BACKGROUND (all pathways)				
Rural - Typical	0.002	0.06	0.003	0.07
Rural - High End	0.01	0.3	0.01	0.3
Urban - Typical	0.002	0.06	0.003	0.07
Urban - High End	0.01	0.3	0.01	0.3
SOURCE-SPECIFIC DOSES				
Tobacco Smoke				
ETS (nonsmoker's dose)	0.0007	0.02	0.0008	0.02
Mainstream (smoker's dose)	0.09	2	0.09	2
Refueling				
Typical	0.00009	0.002	0.0001	0.002
High End	0.001	0.03	0.001	0.03
Occupational				
Typical	0.07[b]		0.08[b]	
High End	0.3[b]		0.3[b]	
BACKGROUND PLUS REFUELING				
Rural - Typical	0.003	0.06	0.003	0.07
Rural - High End	0.01	0.3	0.01	0.3
Urban - Typical	0.003	0.06	0.003	0.07
Urban - High End	0.01	0.3	0.01	0.3

(footnotes on following page)

Table 8.5. (cont.)

Notes:

-- – No value calculated because no benzene exposures are applicable to this category for this age group.

Hazard quotient [HQ] = Average Daily Dose / Reference Dose

Average daily doses are summarized in Table 7.53.

Reference doses used for calculations in this table are presented in Table 8.2.

ETS – environmental tobacco smoke

[a] Noncancer HQs are calculated using the IRIS RfD (labeled High) and Alternative 3 RfD (labeled Low). See Tables 8.1,8.2, and text.

[b] Value is calculated using the occupational threshold limit value (TLV) instead of a reference dose. See Table 8.2 and text for details.

Table 8.6. Cancer risk estimates associated with benzene exposures

Potential excess cancer risks calculated using a range of CSFs. Estimates provided for males and females based on lifetime average daily doses.

	Cancer Risk Estimate (unitless)					
	Using Lower-Bound Nonlinear Model CSF		Using Lower-Bound Linear Model CSF		Using Upper-Bound Linear Model CSF	
	Female	Male	Female	Male	Female	Male
INHALATION PATHWAYS						
Outdoor air (ambient, total)						
Rural - Typical	1E-09	1E-09	9E-08	1E-07	3E-07	3E-07
Rural - High End	2E-09	2E-09	1E-07	1E-07	5E-07	5E-07
Urban - Typical	3E-09	3E-09	2E-07	2E-07	7E-07	8E-07
Urban - High End	7E-09	7E-09	6E-07	6E-07	2E-06	2E-06
Indoor air (in-home, total)						
Typical	5E-08	5E-08	4E-06	4E-06	1E-05	1E-05
High End	2E-07	2E-07	2E-05	2E-05	6E-05	6E-05
In school						
Typical	1E-09	1E-09	1E-07	1E-07	4E-07	4E-07
High End	6E-09	6E-09	5E-07	5E-07	2E-06	2E-06
In vehicle - typical	7E-09	7E-09	5E-07	6E-07	2E-06	2E-06
Showering						
Typical	3E-10	3E-10	2E-08	2E-08	8E-08	8E-08
High End	5E-09	5E-09	4E-07	4E-07	2E-06	2E-06
BACKGROUND						
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)						
Rural - Typical	6E-08	6E-08	4E-06	5E-06	2E-05	2E-05
Rural - High End	2E-07	2E-07	2E-05	2E-05	7E-05	7E-05
Urban - Typical	6E-08	6E-08	4E-06	5E-06	2E-05	2E-05
Urban - High End	2E-07	2E-07	2E-05	2E-05	7E-05	7E-05
Ingestion Pathway (food & water)						
Typical	3E-09	3E-09	2E-07	2E-07	7E-07	7E-07
High End	3E-08	3E-08	3E-06	3E-06	9E-06	9E-06
Occupational - Typical[a]	3E-09	3E-09	2E-07	2E-07	9E-07	9E-07
Occupational - High End[a]	3E-08	3E-08	3E-06	3E-06	1E-05	1E-05
Dermal Pathway (showering)						
Typical	9E-11	9E-11	7E-09	7E-09	3E-08	3E-08
High End	3E-10	3E-10	2E-08	2E-08	8E-08	8E-08
BACKGROUND (all pathways)						
Rural - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Rural - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
Urban - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Urban - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
BACKGROUND (all pathways, including indirect occupational)[a]						
Rural - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Rural - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
Urban - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Urban - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
SOURCE-SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	2E-08	2E-08	1E-06	1E-06	5E-06	5E-06
Mainstream (smoker's dose)	1E-06	1E-06	1E-04	1E-04	4E-04	4E-04
Refueling						
Typical	1E-09	1E-09	1E-07	1E-07	4E-07	4E-07
High End	2E-08	2E-08	1E-06	1E-06	5E-06	5E-06
BACKGROUND PLUS REFUELING						
Rural - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Rural - High End	3E-07	3E-07	2E-05	2E-05	8E-05	8E-05
Urban - Typical	6E-08	6E-08	5E-06	5E-06	2E-05	2E-05
Urban - High End	3E-07	3E-07	2E-05	2E-05	8E-05	9E-05

(footnotes on following page)

Table 8.6. (cont.)

Notes:

Cancer risk estimate = Lifetime Average Daily Dose × Cancer Slope Factor

Lifetime average daily doses are calculated from values presented in Table 7.53, and are time-weighted based on the exposure duration over a 70-yr lifespan.

Cancer slope factors are presented in Table 8.2.

[a] Values represent cancer risk estimates associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.8. Indoor air comparison (in-home): EPA default approach—adults

Results of noncancer risk calculations for in-home indoor air exposures to benzene in the continental United States vs. Alaska for adults.

	Noncancer Hazard Quotients (unitless)[a]			
	19 to <36 yr old female		19 to <36 yr old male	
	Low	High	Low	High
In-Home Indoor Air				
Typical[b]	0.002	0.05	0.002	0.05
High End[b]	0.009	0.2	0.01	0.3
Alaska	0.06	1	0.06	2

Notes:

Hazard quotient [HQ] = Average Daily Dose / Reference Dose
Average daily doses are summarized in Table 7.53.
Reference doses are presented in Table 8.2.

[a] Noncancer HQs are calculated using the IRIS RfD (labeled High) and Alternative 3 RfD (labeled Low). See Tables 8.1, 8.2, and text for details.

[b] Typical and high-end values for the continental United States.

Table 8.9. Noncancer margins of safety associated with benzene exposures—children

Results of noncancer margin of safety for children under various exposure scenarios

	Noncancer Margin of Safety (unitless)					
	<1 yr old	<1 yr old (occup.)[a]	1 to <2 yr old	2 to <6 yr old	6 to <16 yr old	16 to <19 yr old
INHALATION PATHWAYS						
Outdoor air (ambient, total)						
Rural - Typical	38,000	38,000	53,000	22,000	58,000	74,000
Rural - High End	27,000	27,000	38,000	16,000	42,000	53,000
Urban - Typical	17,000	17,000	24,000	10,000	26,000	34,000
Urban - High End	6,200	6,200	8,600	3,600	9,400	12,000
Indoor air (in-home, total)						
Typical	710	710	800	1,100	1,800	2,600
High End	150	150	170	230	390	560
In school						
Typical	--	--	29,000	21,000	16,000	22,000
High End	--	--	6,000	4,300	3,500	4,600
In vehicle - typical	5,500	5,500	6,500	6,600	11,000	14,000
Showering						
Typical	n/a	n/a	22,000	69,000	350,000	480,000
High End	3,200	3,200	1,000	4,300	18,000	26,000
BACKGROUND (summed by pathway)						
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)						
Rural - Typical	620	620	660	830	1,400	1,900
Rural - High End	140	140	140	200	330	470
Urban - Typical	610	610	650	790	1,300	1,900
Urban - High End	140	140	140	190	320	450
Ingestion Pathway (food & water)						
Typical	14,000	2,200	13,000	13,000	32,000	55,000
High End	630	340	840	1,200	2,600	3,700
Dermal Pathway (showering)						
Typical	n/a	n/a	580,000	560,000	830,000	1,000,000
High End	260,000	260,000	200,000	220,000	290,000	350,000
BACKGROUND (all pathways)						
Rural - Typical	590	480	630	780	1,300	1,800
Rural - High End	120	100	120	170	290	420
Urban - Typical	580	470	620	750	1,300	1,800
Urban - High End	110	99	120	160	280	400
SOURCE-SPECIFIC DOSES						
Tobacco Smoke						
ETS (nonsmoker's dose)	1,700	1,700	1,900	2,300	4,300	6,700
Mainstream (smoker's dose)	--	--	--	--	--	120
Refueling						
Typical	--	--	--	--	--	48,000
High End	--	--	--	--	--	4,000
BACKGROUND PLUS REFUELING						
Rural - Typical	590	480	630	780	1,300	1,800
Rural - High End	120	100	120	170	290	380
Urban - Typical	580	470	620	750	1,300	1,700
Urban - High End	110	99	120	160	280	370

(footnotes on following page)

Table 8.9. (cont.)

Notes:

-- – No value calculated because no benzene exposures are applicable to this category for this age group.
n/a – not applicable; exposure was zero for this scenario.
Margin of Safety [MOS] = Point of Departure / Average Daily Dose
Average daily doses are summarized in Table 7.53.
Point of departure is presented in Table 8.3.
Values are rounded to two significant figures.

[a] Values represent hazard quotients associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.10. Noncancer margins of safety associated with benzene exposures—adult

Results of noncancer margin of safety for adults under various exposure scenarios

	Noncancer Margin of Safety (unitless)	
	19 to <36 yr old female	19 to <36 yr old male
INHALATION PATHWAYS		
Outdoor air (ambient, total)		
Rural - Typical	120,000	110,000
Rural - High End	89,000	81,000
Urban - Typical	56,000	51,000
Urban - High End	20,000	18,000
Indoor air (in-home, total)		
Typical	2,500	2,300
High End	540	500
In school		
Typical	--	--
High End	--	--
In vehicle - typical	18,000	16,000
Showering		
Typical	880,000	880,000
High End	46,000	46,000
BACKGROUND (summed by pathway)		
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)		
Rural - Typical	2,200	2,000
Rural - High End	520	470
Urban - Typical	2,100	1,900
Urban - High End	510	470
Ingestion Pathway (food & water)		
Typical	49,000	49,000
High End	4,000	4,000
Dermal Pathway (showering)		
Typical	1,200,000	1,200,000
High End	390,000	390,000
BACKGROUND (all pathways)		
Rural - Typical	2,100	1,900
Rural - High End	460	420
Urban - Typical	2,000	1,900
Urban - High End	450	420
SOURCE-SPECIFIC DOSES		
Tobacco Smoke		
ETS (nonsmoker's dose)	7,200	6,600
Mainstream (smoker's dose)	56	56
Refueling		
Typical	58,000	53,000
High End	4,700	4,300
Occupational		
Typical	69	63
High End	20	18
BACKGROUND PLUS REFUELING		
Rural - Typical	2,000	1,800
Rural - High End	420	390
Urban - Typical	2,000	1,800
Urban - High End	410	380

(footnotes on following page)

Table 8.10. (cont.)

Notes:

-- – No value calculated because no benzene exposures are applicable to this category for this age group.

n/a – not applicable; exposure was zero for this scenario.

Margin of Safety [MOS] = Point of Departure / Average Daily Dose

Average daily doses are summarized in Table 7.53.

Point of departure is presented in Table 8.3.

Values are rounded to two significant figures.

[a] Values represent hazard quotients associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.11. Indoor air comparison (in-home): noncancer margins of safety—children

Results of noncancer margin of safety analysis for children exposed to indoor air.

	Noncancer Margin of Safety (unitless)				
	<1 yr old	1 to <2 yr old	2 to <6 yr old	6 to <16 yr old	16 to <19 yr old
In-Home Indoor Air					
Typical[a]	710	800	1,100	1,800	2,600
High End[a]	150	170	230	390	560
Alaska	25	53	69	110	150

Notes:
Margin of Safety [MOS] = Point of Departure / Average Daily Dose
Average daily doses are summarized in Table 7.53.
Points of departure are presented in Table 8.3.
Values are rounded to two significant figures.

[a] Typical and high-end values for the continental United States.

Table 8.12. Indoor air comparison (in-home): noncancer margins of safety—adults

Results of noncancer margin of safety analysis for adults exposed to indoor air.

	Noncancer Margin of Safety (unitless)	
	19 to <36 yr old female	19 to <36 yr old male
In-Home Indoor Air		
Typical[a]	2,500	2,300
High End[a]	540	500
Alaska	88	80

Notes:
Margin of Safety [MOS] = Point of Departure / Average Daily Dose
Average daily doses are summarized in Table 7.53.
Points of departure are presented in Table 8.3.
Values are rounded to two significant figures.

[a] Typical and high-end values for the continental United States.

Table 8.13. Cancer margins of safety associated with benzene exposures

Results of cancer margin of safety analysis for the general population under various exposure scenarios.

	Cancer Margin of Safety (unitless)	
	Female	Male
INHALATION PATHWAYS		
Outdoor air (ambient, total)		
Rural - Typical	13,000	12,000
Rural - High End	9,400	9,000
Urban - Typical	6,000	5,700
Urban - High End	2,100	2,000
Indoor air (in-home, total)		
Typical	330	310
High End	72	68
In school		
Typical	11,000	11,000
High End	2,400	2,400
In vehicle - typical	2,300	2,100
Showering		
Typical	57,000	57,000
High End	2,800	2,800
BACKGROUND		
Inhalation Pathway (indoor & outdoor air, showering, in-vehicle)		
Rural - Typical	280	260
Rural - High End	66	63
Urban - Typical	270	260
Urban - High End	65	61
Ingestion Pathway (food & water)		
Typical	6,000	6,000
High End	480	480
Occupational - Typical[a]	5,000	5,000
Occupational - High End[a]	450	450
Dermal Pathway (showering)		
Typical	170,000	170,000
High End	56,000	56,000
BACKGROUND (all pathways)		
Rural - Typical	260	250
Rural - High End	58	55
Urban - Typical	260	240
Urban - High End	57	54
BACKGROUND (all pathways, including indirect occupational)[a]		
Rural - Typical	260	250
Rural - High End	58	55
Urban - Typical	260	240
Urban - High End	56	54
SOURCE-SPECIFIC DOSES		
Tobacco Smoke		
ETS (nonsmoker's dose)	880	840
Mainstream (smoker's dose)	12	12
Refueling		
Typical	12,000	11,000
High End	970	890
BACKGROUND PLUS REFUELING		
Rural - Typical	260	240
Rural - High End	55	52
Urban - Typical	250	240
Urban - High End	54	51

(footnotes on following page)

Table 8.13. (cont.)

Notes:
Cancer Margin of Safety [MOS] = Point of Departure / Lifetime Average Daily Dose
Lifetime average daily doses are calculated from values presented in Table 7.53, and are time-weighted based on the exposure duration over a 70-yr lifespan.
Point of departure is presented in Table 8.3.
Values are rounded to two significant figures.

[a] Values represent cancer risk estimates associated with an infant ingesting human milk from a mother who is occupationally exposed to benzene, in addition to other applicable background exposures.

Table 8.14. Indoor air comparison (in-home): margins of safety

Results of cancer margin of safety analysis for exposures to indoor air.

	Cancer Margin of Safety (unitless)	
	Female	Male
In-Home Indoor Air		
Typical[a]	330	310
High End[a]	72	68
Alaska	14	13

Notes:
Margin of Safety [MOS] = Point of Departure / Lifetime Average Daily Dose
Points of departure are presented in Table 8.3.
Lifetime average daily doses are calculated from values presented in Table 7.53, and are time-weighted based on the exposure duration over a 70-yr lifespan.
Values are rounded to two significant figures.

[a] Typical and high-end values for the continental United States.

8.4 Analysis of Risk Assessment Results

Risk assessment is an important tool that should illuminate choices, costs and priorities so public health officials can make informed decisions to protect public health. However, risk assessment is an inexact science. Many layers of conservatism are built into both the exposure assessment component and in the dose-response component where the "acceptable" exposure guideline is developed. Therefore, it is often helpful to conduct reality checks, on both the exposure assessment and the risk assessment findings to see if they make sense. The exposure assessment in this VCCEP report contains a reality check where published blood benzene biomonitoring levels were compared with predicted blood benzene concentrations (using a PBPK model and the estimated exposures from the exposure assessment). The following are some reality checks which are provided to illuminate the reasonableness of the findings from this risk assessment.

8.4.1 Incidence of Childhood Leukemia Is Increasing, Yet Levels of Benzene Are Decreasing

As summarized in Section 5.4, levels of benzene in the environment have declined substantially since the early 1970s and dramatically over the past 15 years. If benzene were to be causing increased incidences of leukemia (and specifically AML) among children, then we would expect to see some decline in the incidence of childhood leukemia in the U.S. that paralleled this decline in environmental benzene. However, the opposite is true; there has been a substantial increase in the incidence of childhood leukemia in the U.S. Most of this increase is attributed to a rise in the incidence of ALL among children. The incidence of AML, which is the most applicable to benzene exposures, among children has remained largely unchanged over the past 30 years (Ries et al., 1999).

This raises some important questions about the current theories for the causes of childhood leukemia. However, the opposing trends between historical benzene exposures and the changes in childhood leukemia incidence suggests that environmental benzene exposures are not a significant contributor towards the background incidence of childhood leukemia in the U.S.

8.4.2 Incidence of Leukemia and AML In Alaska Are No Different Than in the Continental U.S.

The available exposure information on Alaskan homes indicates that they have the potential for significantly higher indoor benzene levels than in homes in the Continental U.S. (section 7.2.1.5). The EPA default (linear) approach would predict that there should be an excess incidence of AML in Alaska compared to the rest of the U.S. This possibility was investigated by analyzing the Alaska cancer registry (Alaska, 2000a; 2000b). The reports for 1997 (Alaska, 2000a) and 1998 (Alaska 2000b) contain incidence and mortality data on specific leukemia subtypes. The Alaska reports provide age-adjusted rates of incidence and mortality (per 100,000 individuals) and confidence intervals for each and the incidence and mortality rate for the continental U.S. for each leukemia subtype. In the 1997 report, the cancer incidence for leukemias were broken

into subtypes of origin of cell-line (myeloid, lymphocytic, moncytic, other) but did not differentiate between acute or chronic. The incidence of myeloid leukemias in 1997 in Alaska was 3.9 per 100,000 (95% CI: 2.2 - 6.6) and the US rate for the years 1993-1997 was reported as 4.4 per 100,000 (Alaska 2000a), suggesting no significant difference between the two. The report for the 1998 cancer registry provided more refined disease classification which allowed for a comparison of specifically AML, the disease of concern with benzene. The incidence of AML in 1998 in Alaska was 3.3 per 100,000 (95% CI: 1.7 – 5.9) and 2.8 in the U.S. for the years 1994 – 1998, again demonstrating no difference between the incidence of AML in Alaska and the U.S. There appears to be no difference in the incidence of leukemia (the subtypes of leukemia were not broken out in the Alaska report) between whites and Alaska natives (Alaska 2000b). AML incidence data for Alaska is not consistent with the hypothesis that Alaskan children are at higher risk due to increased benzene exposure.

8.5 Risk Characterization Summary

The EPA default (linear) approach of calculating HQs and excess cancer risks contains, as EPA's acknowledges, a significant degree of conservatism. The use of a single value for the HQ and/or CSF inappropriately conveys a level of confidence or certainty about the risk estimates, when in fact the HQ and excess risk predicted using a single point estimate contains a large degree of uncertainty, and usually reflects, as with EPA's benzene IRIS values, the upper end of the conservative range of uncertainty. Rounding to one significant figure does not alleviate this problem. Providing a range of risk estimates though, with some discussion and transparency about the uncertainty involved in the "high" and "low" guidance values (e.g., RfC/RfD and CSF) gives greater insight into the plausibility of risk estimates (HQ and/or excess cancer risks) for a given evaluation.

The use of a range of Reference Values for benzene in this assessment (the range of RfDs is approximately a factor of 30) provides greater insights into the uncertain nature of the noncancer risk estimates and provides the risk manager far more insight into the plausible effects predicted in this benzene risk assessment. Even though EPA provides a range of CSFs for benzene, the range of CSFs chosen by EPA do not adequately reflect the uncertainty about their estimates of cancer risks. Most importantly, EPA has neglected to capture the uncertainty about the dose-response model used to fit the 'Pliofilm' cancer mortality data and thus the "model-dependent" impact on risk estimates at low (environmental) exposures. EPA chose a range of CSFs that represented the most conservative estimates of risk from fitting the Pliofilm cohort. Other dose-response models (that assumed a sublinear dose-response) that were used to fit the Pliofilm mortality data derived risk estimates as much as 300 times lower than the EPA chosen CSFs. Therefore, much of the cancer risk predicted using EPA's default linear approach is largely a function of the low-dose extrapolation model used by EPA. As a result, the cancer risk estimates using EPA's default (linear) approach reflect more on EPA policy decisions than on a realistic biological understanding of cancer risks resulting from background exposures to benzene. The theoretical excess cancer risks predicted using the lower-bound nonlinear model derived CSF helps to provide greater insight on this issue.

The MOS analysis provides a rational and intuitive approach for evaluating the "safety" associated with children's exposures to benzene in the environment. By demonstrating

that exposures are lower than the PODs by several orders of magnitude for most exposure scenarios, this MOS approach indicates that the exposures quantified have a large MOS. Despite the significant predicted benzene exposures in some Alaskan homes, the limited epidemiology data suggests that exposures to benzene in Alaska is not posing an elevated risk of developing AML or other leukemias.

As previously discussed, available epidemiological data strongly support that a threshold exists for benzene's hematopoietic toxicity, including the risk for developing AML. While the actual exposure/dose required for the development of AML is not universally agreed upon, the existence of a threshold for AML is consistent with clinical data obtained from secondary leukemia arising from ionizing radiation and/or chemotherapy and our current understanding of bone marrow patho-physiology and biology. For this reason, the cancer risk associated with benzene exposure was calculated with a MOS approach, predicated on a non-linear dose response relationship for the induction of AML. Additionally, clinical data on leukemia risk associated with the treatment of primary pediatric cancers does not support the hypothesis that children are at increased risk of developing chemically induced AML. As a result, a threshold for the development of AML in adults would likely be the same in children. Moreover, published data on the myelosuppressive/hematotoxic effects of various chemotherapy agents in children and adults does not support the existence of an age related difference in sensitivity. Therefore, additional uncertainty factors were not deemed necessary to adequately assess the risk of benzene associated adverse health effects in children.

Levels of benzene in the ambient environment have declined substantially over the past four decades and are anticipated to continue to decline. Therefore, the estimated margins of safety are anticipated to increase over the coming years and decades.

8.6 References

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